Remarks

By the present amendments, claims 23, 24, 25, 26, 29 and 38 have been amended and claims 30 and 40-56 have been deleted. New claims 57-73 have been added rendering claims 23-29, 31-39 and 57-73 pending in the application. The amendments to the claims have been made without prejudice and without acquiescing to any of the Examiner's objections. The amendment does not contain new matter and its entry is respectfully requested. Applicant reserves the right to pursue any of the deleted subject matter in a further divisional, continuation or continuation-in-part application.

The office action dated July 30, 2002 has been carefully considered. It is believed that the amended claims submitted herewith and the following comments represent a complete response to the Examiner's rejections and place the present application in condition for allowance. Reconsideration is respectfully requested.

We will address each of the items in the office action using the same numbering system used by the Examiner.

1. We note the renumbering of the claims by the Examiner and we have referred to renumbered claims 23-56 herein.

2. Applicants thank the Examiner for withdrawing several of the rejections in the previous office action in view of Applicants' amendments.

35 USC §112, First Paragraph

3. The Examiner has objected to claims 23-39 under 35 USC §112, first paragraph, alleging that the specification does not reasonably provide enablement for a method of increasing the serum half-life of an immune globulin comprising parenterally administering to an animal in need thereof an immune globulin preparation or the use of two or more non-ionic surface active agents in said preparation. We respectfully disagree with the Examiner for the reasons that follow.

The Examiner comments that the specification is enabling for a method comprising the steps of: making an immune globulin preparation; administering the preparation to an animal in need of an immune globulin preparation; and using the pharmacokinetic methods to determine whether or not there is an increase in the estimated half-life of the immune globulin. In view of the Examiner's comments, Applicants have amended claim 23 in order to include the step of making the immune globulin preparation and to specify that the animal is in need of an immune globulin. However, Applicants respectfully submit that the step of using pharmacokinetic methods to determine the serum half-life is not an essential feature of the method and does not need to be listed in the main claim. We submit that the step of measuring the serum half-life does not increase serum half-life of the immune globulin and therefore it is not necessary to achieve the claimed results contrary to the Examiner's assertion on page 4 of the office action. Further, we point out that once the invention is realized by others (by virtue of them having read the present specification), there would be no need to measure the serum half-life after the administration of each preparation. Consequently, including such a step in the claims would unduly reduce the scope of Applicants' claim to which they are entitled.

4. The Examiner has also objected to claims 40-56 under 35 USC §112, first paragraph as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains or to which it is most nearly connected, to make and/or use the invention.

5. The Examiner has further objected to claims 40-56 under 35 USC §112, first paragraph as not meeting the written description requirements.

In response to objections 4 and 5, claims 40-56 have been deleted without prejudice.

In view of the foregoing, we respectfully request that all of the objections to the claims under 35 USC §112, first paragraph, be withdrawn.

35 USC §112, Second Paragraph

6. The Examiner has objected to claims 23-39 under USC §112, second paragraph as being indefinite. Specifically, the Examiner has stated that the term "increase the serum life" in the claims is not defined by the claim. Furthermore, the Examiner has stated that it is unclear how to define the term "increase the serum life". Applicants respectfully submit that the term used in the claims is "increase the serum half-life" (emphasis added). Applicants differ with the view of the Examiner. The term "increase the serum half-life" is defined in the specification of the instant application. The Examiner is kindly directed to page 15 lines 6 to 10 of the instant application that states:

> "The phrase "sufficient to increase the serum half-life of the immune globulin" means that the serum half-life of the immune globulin with at least one surface active agent is increased as compared to the serum half-life of the immune globulin when administered without a surface active agent."

Applicants further direct the Examiner's attention to page 22 line 26 through page 26 line 15 of the instant application. Applicants submit that the above noted pages describe in detail the pharmacokinetic assays to determine if the serum half-life of the immune globulin with at least one surface active agent is increased as compared to the serum half-life of the immune globulin when administered without a surface active agent.

Applicants submit the term "increase the serum half-life" is defined in the instant application and respectfully requests the Examiner allow claims 23-39 as they presently read.

7. The Examiner has stated claims 23 and 40 are unclear as the term "animal in need thereof" does not clearly define whether the animal is in need of the recited methods or the immune globulin preparation. In response, Applicants have deleted

claim 40 without prejudice, and amended claim 23 to specify the animal is in need of the immune globulin. Applicants respectfully submit claim 23, as amended, overcomes the Examiner's objection and respectfully request allowance of claim 23.

8. The Examiner has objected to claims 40-56 as being indefinite. Specifically, the Examiner has stated that the term "to reduce the elevation of neutrophil counts" is not defined. Applicants have deleted claims 40-56 without prejudice.

9. The Examiner has rejected claims 24 and 27 under 35 USC §112, second paragraph. Specifically, the Examiner has stated that the abbreviations anti-Rh_oD and anti-c must be spelled out. In response, Applicants have amended claim 24 and 25 to replace the term anti-Rh_oD with the term anti-D. Applicants submit anti-D is not an abbreviation and is defined on page 15, line 20. Applicants respectfully submit that the term anti-c is not an abbreviation and is defined on page 15, line 20. Applicants respectfully request the Examiner allow claims 24 and 27 as they currently read.

10. The Examiner has rejected claims 26, 29, 38, 43 and 46 as vague. The Examiner has stated that the claims are drawn to a method that is aqueous and unclear. In response, Applicants have amended claims 26, 29 and 38 to specify the immune globulin preparation is aqueous. Applicants have deleted claims 43 and 46 without prejudice. Applicants respectfully submit claims 26, 29 and 38, thus amended, have overcome the Examiner's objections and are ready for allowance.

11. The Examiner has rejected claims 38 and 55 as being indefinite for failing to particularly point out and distinctly claim the subject matter. Specifically, the Examiner has stated that the above noted claims contain a trademark/trade name (Polysorbate 80™). In response, Applicants have amended claim 38 and replaced the term "Polysorbate 80™" with the term "polyoxyethylene sorbitan monooleate". Support for this amendment can be found on page 7, lines 3 to 5 of the instant application which identifies Polysorbate 80™ by its chemical name polyoxyethylene sorbitan monooleate.

The Examiner has also objected to the terms "very low" level buffer and "essentially no ionic strength" in claims 38 and 55, and stated that the above noted terms are relative terms. In response, these terms have been deleted from claim 38. Claim 55 has been deleted.

12. The Examiner has objected to claims 39 and 56 as unclear. Specifically, the Examiner has stated that the claims recite a group consisting of only one member (glyceryl monooleate) and that the glyceryl monooleate is not a non-ionic surfactant. Applicant does not agree with the Examiner. Applicants submit that the claims recite: "the group consisting of glyceryl monooleate; and a polyvinyl alcohol." As such, the group consists of two members.

The Examiner has also stated that glyceryl monooleate is not a non-ionic surfactant. The Examiner's attention is directed to page 6, lines 13 to 17 that describe non-ionic surface active agents as being amphipathic possessing an hydrophilic moiety and a hydrophobic end. The Examiner is further directed to the enclosed Chemical Identification (retrieved form the web site: http://hazard.com/msds/tox/f/q83/q826.html), which identifies glyceryl monooleate as being synonymous with oleoylglycerol. The molecular structure of oleoylglycerol was retrieved from the Sigma Aldrich web page, and is enclosed. The structure conforms to the definition of a surface active agent as the hydrophilic moiety comprises the glyceryl group that has two hydroxyls and an ester group, and the hydrophobic tail comprising the 18 carbon fatty acid. Applicant has deleted claim 56. In view of the foregoing, Applicants respectfully request that the objection to claim 39 be withdrawn.

In view of the foregoing, we respectfully request that all of the objections to the claims under 35 USC §112, second paragraph, be withdrawn.

35 USC §102

13. The Examiner has objected to claims 23, 26, 31-34, 36-37, 40, 43, 47, 49-51 and 53-54 under 35 USC §102(b) as being anticipated by Alberici et al., WO 94/16728. We respectfully disagree with the Examiner for the reasons that follow.

We note that previous claim 30 was not included in the objection. Consequently, claim 23 has been amended to insert the subject matter of previous claim 30. In particular, claim 23 has been amended in order to specify that the immune globulin is present in an amount from about 2 to about 10% by weight of the immune globulin preparation. In contrast, Alberici teaches an antibody formulation with an antibody concentration of 0.01-1.0%, preferably 0.1% by weight.

Applicants have also added a new set of claims numbered 57-73. Claim 57 specifies that the immune globulin is polyclonal immune globulin as Alberici et al. is concerned with monoclonal antibodies only.

In view of the foregoing, we respectfully request that the objection to the claims under 35 USC §102(b) be withdrawn.

35 USC §103

14. The Examiner has rejected claims 23-34, 36-38, 40-51 and 53-55 under 35 USC §103(a) as being unpatentable over Friesen (CA 1,168,152) in view of de Burgh Bradley et al (1,303,533). We respectfully disagree with the Examiner for the reasons that follow.

The Examiner states that de Burgh Bradley et al. (herein after referred to as Bradley et al.) teaches a Solution for Manual Use that includes sodium chloride, distilled water, and TWEEN 20. The Examiner states that combining the immune globulin taught by Friesen with such Solution for Manual Use, results in the invention described in the above claims. Applicant respectfully disagrees with the Examiner. Applicants submit that the Solution for Manual Use taught in Bradley et al can only be used for *in vitro*

testing of blood types and intravenous injection of such solution is fatal. Thus, the combination of Friesen and Bradley et al cannot produce an immune globulin preparation for parenteral administration.

The Examiner has stated that Bradley et al teaches parenterally administrating an immune globulin preparation comprising several of the same reagents as in Friesen, yet advantageously further comprising a non-ionic surface active agent such as Tween 20. Applicants submit the formulation taught by Bradley et al cannot be administered parenterally. Applicants direct the Examiner's attention to page 29, lines 7-20 of Bradley et al, which describes the formulation of the Solution for Manual Use. Applicants note the Solution for Manual Use includes potassium phosphate (line 12) and sodium azide (line 16). Both of these substances are highly toxic and potentially lethal if injected parenterally or intravenously. Applicants submit that the Solution for Manual Use is intended for testing for the Rh-D antigen on red blood cells. The Examiner is directed to Bradley et al page 29, lines 19-20 that states:

> "This blend [Solution for Manual Use] can be used in all manual tests for D and D^U typing, e.g. microtitre, microplate , IAG."

Applicants submit that Bradley et al. does not teach an antibody solution that can increase the serum half-life of an immune globulin as the Solution for Manual Use cannot be injected into an animal. Therefore, the antibody formulation taught by Bradley et al does not teach the serum half-life increasing benefits of Polysorbate 80™.

Applicants have carefully reviewed Bradley et al. and Applicants submit that there is no teaching that the addition of Tween 80™ or any non-ionic surface active agent as being advantageous in immune globulin preparation for parenteral administration.

Applicants submit that combining Friesen with Bradley et al results in an Rh-D immune globulin formulation that can only be used for blood typing experiments *in*

vitro. Applicants have deleted claims 40-51 and 53-55. Applicants respectfully request the Examiner withdraw his objection to claims 23-34 and 36-38 under 35 USC §103(a).

15. The Examiner has rejected claims 39 and 56 under 35 USC §103(a) in view of the combination of Friesen, Bradley and Eibl et al. (U.S. Patent No. 4,276,283). We respectfully disagree with the Examiner for the reasons that follow.

The Examiner states that Eibl teaches an immune globulin formulation that includes polyvinyl alcohol. Applicants respectfully disagree with the Examiner. Applicants submit that Eibl teaches a method of purifying immune globulins from human blood (Eibl, Column 1, lines 8 to 15). Polyvinyl alcohol is used as a precipitating agent, but is not intended to be present in the final pharmaceutical preparation. Applicants note Eibl, Claim 1, step f, and column 3 lines 36 to 49:

> "As soon as the purification of the immune globulins has been effected in the manner described, these can be recovered from the solution, i.e. by precipitation with water-soluble polymers. From these, copolymers of ethylene oxide and polyoxypropylene (trade name of BASF "PLURONIC"), and dextrane, polyvinyl alcohol, polyvinyl pyrrolidone and the like have proved successful. It is also possible to use polyethylene glycol as the precipitating agent for the pure immune globulin by increasing the concentration of the polyethylene glycol in the remaining solution to more than 150 g/l. The immune globulin precipitated is then processed into the pharmaceutical preparation, known measures being applicable."

Applicants submit that the polyvinyl alcohol is only used as a precipitating agent and is not intended to be present in any significant amount in the final, processed pharmaceutical preparation. Applicant notes Eibl et al column 3, lines 50 to 56 that further describes how the precipitated immune globulin is formulated into a pharmaceutical preparation by "further dialysis, ultrafiltration or gel filtration,

adjustment of immune globulin concentration ... and regulation of the ionic strength." Gel filtration is a method of separating substances based on their size. An immune globulin is considerable larger that a polyvinyl alcohol, and would not exit a gel filtration column in the same fraction as polyvinyl alcohol. Furthermore, the final immune globulin formulation is adjusted for immune globulin concentration and ionic strength. No mention is made as to the concentration of polyvinyl alcohol. Applicants have carefully reviewed Eibl et al. and submit there is no teaching of a pharmaceutical preparation containing immune globulins and polyvinyl alcohol.

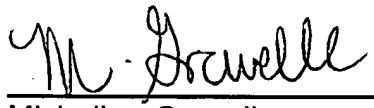
Applicants' comment on Bradley et al appear above. Applicants submit that the combination of Friesen, Bradley et al and Eibl et al do not teach the invention described in claim 39. Applicants have deleted claim 56. In view of the foregoing, we respectfully request that the objection to claim 39 under 35 USC §103 be withdrawn.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made".

Should the Examiner deem it beneficial to discuss the application in greater detail, he is kindly requested to contact the undersigned by telephone at (416) 364-7311 at his convenience.

Respectfully submitted,

Hugh W. Price and B. Michael R. Woloski



Micheline Gravelle
Registration No. 40,261

Bereskin & Parr
Box 401, 40 King Street West
Toronto, Ontario Canada M5H 3Y2
(416) 364-7311

Version with markings to show changes made

In the Claims:

Claims 23, 24, 25, 26, 29 and 38 have been amended as follows:

23. (Amended) A method of increasing the serum half-life of an immune globulin comprising: [parenterally administering to an animal in need thereof an immune globulin preparation comprising]

(a) combining [an] the immune globulin and at least one non-ionic surface active agent[,] into an immune globulin preparation wherein the concentration of the immune globulin is about 2 weight percent to about 10 weight percent of the preparation and wherein said one or more non-ionic surface active agent(s) is in a concentration sufficient to increase the serum half-life of the immune globulin; and

(b) parenterally administering the immune globulin preparation to an animal in need of the immune globulin.

24. (Amended) A method according to claim 23 wherein the immune globulin is [anti-Rh_oD] anti-D immune globulin.

25. (Amended) A method according to claim 24 wherein the [anti-Rh_oD] anti-D immune globulin has an IgG purity of greater than about 95% and a monomeric protein content of greater than about 94%.

26. (Amended) A method according to claim 25 wherein the immune globulin preparation is an [which is] aqueous formulation.

29. (Amended) A method according to claim 28 wherein the immune globulin preparation is an [which is] aqueous formulation.

38. (Amended) A method according to claim 23 wherein the immune globulin preparation comprises:

about 3-8% human [anti-Rh_oD] anti-D immune globulin with an IgG purity of greater than 95% and a monomeric protein content of greater than 94%;

sodium chloride at about 0.25% (w/v);

[very low level buffer with essentially no ionic strength;]

polyoxyethylene sorbitan monooleate [Polysorbate 80"] at about 0.01% to about 0.5% (w/v); and

L-glycine at about 0.1M.

Claims 30 and 40-56 have been deleted.

New claims 57-73 have been added as follows:

57. (New) A method of increasing the serum half-life of a polyclonal immune globulin comprising:

(a) combining the polyclonal immune globulin and at least one non-ionic surface active agent into an immune globulin preparation, wherein said one or more non-ionic surface active agent(s) is in a concentration sufficient to increase the serum half-life of the polyclonal immune globulin; and

(b) parenterally administering the immune globulin preparation to an animal in need of the immune globulin.

58. (New) A method according to claim 57 wherein the immune globulin is anti-D immune globulin.

59. (New) A method according to claim 58 wherein the anti-D immune globulin has an IgG purity of greater than about 95% and a monomeric protein content of greater than about 94%.

60. (New) A method according to claim 59 wherein the immune globulin preparation is an aqueous formulation.

61. (New) A method according to claim 57 wherein the immune globulin is anti-c immune globulin.

62. (New) A method according to claim 61 wherein the anti-c immune globulin has an IgG purity of greater than about 95% and a monomeric protein content of greater than about 94%.

63. (New) A method according to claim 62 wherein the immune globulin preparation is an aqueous formulation.

64. (New) A method according to claim 57 wherein the concentration of the immune globulin is about 2 weight percent to about 10 weight percent.

65. (New) A method according to claim 57 wherein the one or more non-ionic surface active agent(s) is(are) a sorbitan ester of a fatty acid.

66. (New) A method according to claim 65 wherein the non-ionic surface active agent(s) is(are) selected from the group consisting of sorbitan monolaurate, sorbitan monopalmitate, sorbitan monostearate, sorbitan tristearate, sorbitan monooleate, and sorbitan trioleate.

67. (New) A method according to claim 65 wherein the one or more non-ionic surface active agent(s) is(are) a polyoxyethylene sorbitan ester of a fatty acid.

68. (New) A method according to claim 67 wherein the non-ionic surface active agent(s) is(are) selected from the group consisting of polyoxyethylene (20) sorbitan monolaurate, polyoxyethylene (4) sorbitan monolaurate, polyoxyethylene (20) sorbitan monopalmitate, polyoxyethylene (20) sorbitan monostearate, polyoxyethylene (4) sorbitan monostearate, polyoxyethylene (20) sorbitan tristearate, polyoxyethylene (20) sorbitan monooleate, polyoxyethylene (5) sorbitan monooleate, and polyoxyethylene (20) sorbitan trioleate.

69. (New) A method according to claim 57 wherein two or more non-ionic surface active agents are selected from the group consisting of polyoxyethylene (20) sorbitan monolaurate, polyoxyethylene (4) sorbitan monolaurate, polyoxyethylene (20) sorbitan monopalmitate; polyoxyethylene (20) sorbitan monostearate, polyoxyethylene (4) sorbitan monostearate, polyoxyethylene (20) sorbitan tristearate, polyoxyethylene (20) sorbitan monooleate, polyoxyethylene (5) sorbitan monooleate, and polyoxyethylene (20) sorbitan trioleate, sorbitan monolaurate, sorbitan monopalmitate, sorbitan monostearate, sorbitan tristearate, sorbitan monooleate, and sorbitan trioleate.

70. (New) A method according to claim 57 wherein the concentration of the one or more non-ionic surface active agent(s) is(are) about 0.01 weight percent to about 0.5 weight percent.

71. (New) A method according to claim 57 wherein the immune globulin preparation is a lyophilized preparation.

72. (New) A method according to claim 57 wherein the immune globulin preparation comprises:

about 3-8% human anti-Dimmune globulin with an IgG purity of greater than 95% and a monomeric protein content of greater than 94%;

sodium chloride at about 0.25% (w/v);

polyoxyethylene sorbitan monooleate at about 0.01% to about 0.5% (w/v); and

L-glycine at about 0.1M.

73. (New) A method according to claim 57 wherein the one or more non-ionic surface agents are selected from the group consisting of glyceryl monooleate; and a polyvinyl alcohol.

*** CHEMICAL IDENTIFICATION ***

RTECS NUMBER : RK1300000
CHEMICAL NAME : Olein, mono-
CAS REGISTRY NUMBER : 25496-72-4
LAST UPDATED : 199701
DATA ITEMS CITED : 5
MOLECULAR FORMULA : C21-H40-O4
MOLECULAR WEIGHT : 356.61
COMPOUND DESCRIPTOR : Primary Irritant
SYNONYMS/TRADE NAMES

* Adchem GMO
* AJAX GMO
* Aldo 40
* Aldo MO-FG
* Dur-Em 204
* Emcol O
* Emery oleic acid ester 2221
* Emrite 6009
* Glycerine monooleate
* Glycerin monooleate
* Glycerol monooleate
* Glycerol oleate
* Glyceryl monooleate
* Glyceryl oleate
* GMO 8903
* Harowax L 9
* Loxiol G 10
* Monoglyceryl oleate
* Monoolein
* Monooleoylglycerol
* 9-Octadecenoic acid (Z)-, monoester with 1,2,3-propanetriol
* Oleic acid glycerol monoester
* Oleic acid monoglyceride
* Oleoylglycerol
* Oleylmonoglyceride
* Olicine
* Rikemal O 71D
* Rikemal ol 100
* S 1096
* S 1097
* Sinnoester ogc
* S 1096R
* Sunsoft O 30B
* Supeol

*** HEALTH HAZARD DATA ***

** SKIN/EYE IRRITATION DATA **

TYPE OF TEST : Standard Draize test
ROUTE OF EXPOSURE : Administration onto the skin
SPECIES OBSERVED : Rodent - rabbit
DOSE/DURATION : 500 mg
REACTION SEVERITY : Mild
REFERENCE :
JACTDZ Journal of the American College of Toxicology. (Mary Ann Liebert, Inc., 1651 Third Ave., New York, NY 10128) V.1-12, 1982-1993. Discontinued
Volume(issue)/page/year: 5(5),391,1986

TYPE OF TEST : Standard Draize test
ROUTE OF EXPOSURE : Administration into the eye
SPECIES OBSERVED : Rodent - rabbit
DOSE/DURATION : 100 mg
REACTION SEVERITY : Mild
REFERENCE :
JACTDZ Journal of the American College of Toxicology. (Mary Ann Liebert, Inc., 1651 Third Ave., New York, NY 10128) V.1-12, 1982-1993. Discontinued
Volume(issue)/page/year: 5(5),391,1986

*** NIOSH STANDARDS DEVELOPMENT AND SURVEILLANCE DATA ***

NIOSH OCCUPATIONAL EXPOSURE SURVEY DATA :
NOHS - National Occupational Hazard Survey (1974)
NOHS Hazard Code - 83110
No. of Facilities: 4016 (estimated)
No. of Industries: 41
No. of Occupations: 51
No. of Employees: 74220 (estimated)

NOES - National Occupational Exposure Survey (1983)
NOES Hazard Code - 83110
No. of Facilities: 9941 (estimated)
No. of Industries: 81
No. of Occupations: 78
No. of Employees: 159120 (estimated)
No. of Female Employees: 39063 (estimated)

*** STATUS IN U.S

EPA TSCA Section 8(b) CHEMICAL INVENTORY

** END OF RECORD ***

Product Number: **M2787**
Product Name: **2-Oleoylglycerol**

Product Information
Price/Availability
Certificate of Analysis
Certificate of Origin
MSDS
Structure Image
Options
Print Preview
Bulk Quote
Ask A Scientist